Universidade de Lisboa

Faculdade de Farmácia

Evaluation of the ability of milk to act as coating agent in paediatric formulations

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Mestrado Integrado em Ciências Farmacêuticas

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RESUMO

Neste trabalho, o leite é proposto como excipiente inovador (agente de revestimento), para formulações pediátricas como agente mascador de sabor. Foram produzidos, por extrusão-esferonização, *pellets* constituídos por celulose Microcristalina e Paracetamol. O Paracetamol está descrito na literatura como substância ativa segura, integrando a lista de fármacos essenciais para uso pediátrico, elaborada pela Organização Mundial de Saúde. Foram realizadas três formulações distintas de revestimento com diferentes tipos de leite de vaca – leite magro, leite meio gordo e leite gordo – avaliando-se a capacidade de funcionarem como agentes de revestimento. O processo de revestimento foi realizado em equipamento de leito fluidizado, usando a configuração de *Wurster*. A influência das variáveis do processo - volume e temperatura do ar, pressão de atomização do ar e temperatura do produto- foi investigada pelo seu impacto na qualidade da camada de revestimento formada. As características da superfície dos *pellets* revestidos, bem como a espessura da camada de revestimento foi analisada qualitativamente por Microscopia de Varrimento (SEM). Características organoléticas, como o odor, cor e sabor foram igualmente avaliadas. Um lote de controlo foi produzido, com a mesma composição e tamanho de partícula, para posterior comparação com os *pellets* revestidos. Tanto os *pellets* revestidos como os sem revestimento (controlo) foram caracterizados em termos de teor de substância ativa, perfil de dissolução, *aspect ratio*, friabilidade e teor de perda por secagem. Durante o processo de revestimento, parâmetros como o volume e temperatura de ar de entrada foram difíceis de manter constantes culminando numa camada de revestimento pouco espessa e heterogénea, com fissuras visíveis nas imagens obtidas por SEM. A proteína do leite, caseína, formou micelas que prenderam a substância ativa e assim, diminuíram o teor de substância ativa. Os resultados dos testes de friabilidade, perda por secagem, *aspect ratio* e perfil de dissolução não sofreram variações significativas com a camada de revestimento. Os *pellets* revestidos apresentavam sabor, cheiro e cor característicos do leite, mostrando que o revestimento aderiu à superfície dos *pellets*. O estudo provou que o leite tem a capacidade de funcionar como agente mascarador de sabor, no entanto a formulação de revestimento tem de ser melhorada, por exemplo adicionando um anti- aderente, como o Talco, e um plasticizante, como o Sorbitol.

Palavras-chave: Leite, Paracetamol, Pediátrico, *Pellet*, Revestimento.

ABSTRACT

In this work, milk is proposed as a novel excipient (coating agent) in paediatric formulations as taste-masking agent. Pellets were conducted with Microcrystalline Cellulose and Paracetamol, a drug with a safety described in literature, part of the World Health Organizations (WHO) lists of essential medicines for children, as nuclei made by extrusion-spheronization. Three coating films were made with different types of cow's fresh milk - skimmed milk; half-fat milk; fat milk - and its ability to function as film-forming agent were evaluated. The coating process was performed in a fluidized bed system, using the Wurster configuration. The influence of the process variables – volume and temperature of the inlet air, atomization air pressure and temperature of the product - on the quality of the coating layer was investigated. The surface characteristics of the coated pellets and the thickness of the coating film were analysed qualitatively by Scanning Electron Microscopy (SEM). Organoleptic characteristics were also evaluated, such as odour, colour and taste. A control batch, with the same granulometric class, composition and without coating film was made in order to compare the effect of the coating layer. Both coated and uncoated pellets (control) were characterized in terms of drug content, dissolution profile, aspect ratio, friability and loss on drying. During the coating process, parameters like the volume of inlet air and temperature were hard to maintain which led to a thin and heterogenous coating layer full of cracks ,visible in SEM images. Casein, a milk protein, formed micelles and entrapped the drug substance, decreasing the drug content. Friability, loss on drying, aspect ratio and the dissolution rate did not suffer significant variations with the milk film. Coated pellet's taste, odor and colour was characteristic of milk, proving that milk film adhered to the pellet surface. The study proved that milk is suitable to function as taste-masking agent, however the coating formulation has to be improved by adding, for example, an anti-adherent, as Talc, and a plasticizer, such as Sorbitol.

Keywords: Coating, Milk, Paediatrics, Paracetamol, Pellet.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

1. STATE OF THE ART

1.1. Paediatric Formulations

Paediatric population englobes new-borns to adolescents, with multiple differences in terms of pharmacodynamic and pharmacokinetics according to age (1). The lack of formulations aimed for paediatric use is one of the biggest flaws of pharmaceutical industry, which leads to the prescription of unlicensed or off-label drugs and to the increase necessity to manipulate a medicine, developed for adult, to achieve the require dose (2).

The World Health Organization (WHO) created a list of essential medicines for children up to 12 years of age, called *Who Model List of Essential Medicines for Children*. This list includes indications of safety, cost-effectiveness, efficacy and priority conditions for drugs considered the minimal requirements for a basic-care system for paediatric population, selected based on current and estimated future public health relevance and potential for safe and cost-effective treatment (3).The need to create this list comes from the fact that children cannot be considered and treated as little adults. Children need specific dosages and formulations according to their weight and biological characteristics (4). Children differ from adults in several ways, especially considering pharmacokinetic and pharmacodynamic parameters: they ingest, absorb, metabolize and excrete drugs using different mechanisms from adults. Also, some issues regarding children behaviour and development can influence, and even complicate, their treatment (3). World Health Organization is perfectly aware of the challenge that is developing a formulation for paediatric population that is safe and appropriate for all paediatric age groups , thus, the main ambition is to develop formulations flexible in terms of dosage to be suitable for the maximum age range possible (1) due to the pharmacodynamic and pharmacokinetic profiles that fluctuate depending on the age and weight of a child (5).

Another fundamental point regarding paediatric population and medicine is the acceptability by the child. Acceptability of the pharmaceutical form is essential for adherence to therapy. Palatability, swallowability, proper dose, dose frequency, duration of the treatment, administration device, appropriate packaging and enlightening labelling information are crucial factors that influence the acceptability of medicines by children. The acceptability of a dosage form by parents and caregivers is also necessary and it may represent a challenge. In several cases, cultural believes can represent a barrier to adherence to therapeutics (1). Palatability of oral formulations often determinates the child's compliance (6) and it is defined as the appreciation of a medicinal product by organoleptic properties such as smell, taste, aftertaste and the texture of the drug, and it depends on the characteristics of the active pharmaceutical

ingredient (API), excipients and the drug formulation itself (7). Children are able to recognize different tastes from young age and it is a well-known fact that children have a bigger preference for sweeter taste and a greater rejection for bitter taste (7). The bitter taste of some APIs affects the palatability and consequently acceptance of the therapeutic, mostly in this target group (6). Parents and caregivers often tend to mask the unpleasant taste of medicinal products with food or juice, in order to enhance the child compliance. Although it may mask the bitter taste of the pharmaceutical formulation, this can have a detrimental effect on efficacy and safety (2). In this sense, masking bitterness of certain APIs is an important step in the drug development for paediatric use. Developing an acceptable and tasteful paediatric oral dosage form, compliant with all global regulations, may represent a challenge due to restrictions in availability of excipient types and quantity (1). Furthermore, maintaining the pharmacokinetic profile and masking the bitter taste of a drug can be a challenging task (8). Flavours and sweeteners are the excipients most frequently utilized to mask the bitter taste of an API in paediatric formulations. Conventionally, the taste chosen to mask the bitter taste of an API must be accepted by as many cultures as possible (1). However, it is necessary to pay attention to special conditions, such as diabetes, fructose intolerance or excipients that may be toxic to children. It should also be taken in consideration that a too palatable medicine can led to overdosing (9). The European Medicines Agency (EMA) recognises the importance of formulating oral formulations with acceptable palatability for paediatric populations (7).

Another important factor that influences child's compliance to the therapeutic is the pharmaceutical form. When the pharmaceutical form is chosen it should take into account the balance between risk and benefit, never forgetting the special needs of the target population (1). Oral liquid formulations are the most preferable formulations for children who are not able or willing to swallow (10). Besides that, oral liquid formulations offer high dose flexibility, meaning that it is possible to measure and administer several volumes according to children's weight and age. However, they also present disadvantages such as the need to use chemical and microbial stabilizers, are less practical to carry in comparison to solid forms because of the higher volume (1), as well as the lack of controlled released liquid formulations (10). In contrast, solid formulations present an improved biological stability, precision of dose and an easier transportation because of their minor volume when compared with liquid forms. Furthermore, oral solid formulation allow the development of modified-release formulations (10). Oral solid formulations represent the majority of pharmaceutical forms in the pharmaceutical industry. However, in paediatric population, solid forms are not easily accepted (5). There is a high probability that children may not be willing or able to swallow an oral solid

formulation, even when the pharmaceutical form is considered suitable for that age. The ability of a child to swallow a tablet is directly connect with its size, shape and palatability (11). An alternative to enhance children's swallowability of tablets that should be considered is to create breaking lines on tablets to allow tablets breakage (10). Furthermore, education and training by parents and caregivers are crucial to improve the capacity of children to swallow solid dosage forms (5). A problem related to solid forms is the lack of appropriate dosages according to the children's age and weight. In this sense, often tablets have to be broken to adjust the dose to the children's weight (12). However, breaking tablets can led to inefficacy of the medicinal product, dosage errors (9) or /and cause adverse reactions (13).

The increased need to create acceptable and appropriate medicines for children led to new approaches in formulation design, like pellets (12) and granules (13). One advantage of these multi-unit dosage forms is the increased dose flexibility. Each subunit contains a small amount of the active substance, thereby the dose can be adjusted by measuring a specific weight of these subunits according to the body weight of the patient (12). Another advantages is the easy swallowing due to their reduced size (5) . Studies have shown that children over 6 months are physically and anatomical able to swallow pellets. Plus, multi-unit dosages forms are suitable for taste-masking, in case of a bitter tasting API, improving children's acceptability, and for controlled release modifications using coating techniques (5).

1.2. Multi-unit dosage forms

Pellets and granules are multiparticulate dosage forms consisting of several small subunits, each containing the drug substance. In these multi-unit dosage forms, the dose is the sum of the quantity of API of each subunit. These multiple subunits are normally filled into a sachet, compressed in order to form a tablet, or encapsulated. Multi-unit dosage forms present several advantages, such as: improved disintegration and distribution, better bioavailability due to the greater distribution in the GI, decreased risk of systemic and local toxicity (14) due to the fact that after administration subunits spread uniformly in the gastrointestinal tract, resulting in a consistent drug release with reduced risk of local irritation and toxicity and also minimised side effects (15). Multiparticulate systems have an improved dissolution profile in-vivo, resulting in better bioavailability (16). Moreover, multi-unit dosage forms can be easily coated and allow high flexibility during the development of the formulation (16). For the paediatric population, these multi-unit dosage forms offer easier ingestion when compared to tablets or capsules. One disadvantage of these pharmaceutical forms is that its small size can be a critical

factor to initiate a chewing response when administered to children, and this can be particularly worrying in modified release forms (17).

1.2.1. Pellets

Pellets are defined as free-flowing, small and spherical particles, manufactured by agglomeration of powders or granules, constituted by drug substance and excipients, using an appropriate equipment. Besides free-flowing properties, pellets also have low porosity (about 10%) (18). Pellets are used in different industries like agriculture (herbicides and fertilizers), mineral processing (iron ore pelletization), detergent, food and pharmaceutical industry (19). In the pharmaceutical field, pellets can be filled into capsules, compressed to form tablets or added to a suspension. Normally, pellets size ranges from 500 to 2000 μm (20). Pellets offer several advantages when compared with traditional unit-dose systems, both technologically and therapeutically, namely great flow properties, improved bioavailability, are easy of swallowing, allow dose flexibility, have low risk of dose dumping, allow the development of controlled-released formulations and flexibility of mixing different release profiles with different drug substances, present free dispersion through the gastrointestinal tract- which leads to a maximized drug absorption, as a bigger gastrointestinal surface is involved- and the large distribution of the subunits in the gastrointestinal tract decreases the local irritation of the gastrointestinal mucosa and systemic toxicity of some drugs (18). However, disadvantages regarding the use of pellets also exist, such as the high cost inherent to the necessity of specialized equipment, thus increasing the manufacturing costs. During the manufacturing process there are several variables that need to be controlled, which complicate the process (18).

1.3. Coating

Coating is an extra step in the development of a medicinal drug (21) which allows the development of controlled-released formulations, protecting the API from the acid environment of the stomach or even prevent the irritation of the gastric mucosa by the API .The coating film may contain the API in the formulation itself. This type of coating is used to develop formulations with different drugs, and this way prevent interaction between the different APIs, or to combine different release profiles in just on single used to enhance the patient compliance by improving organoleptic characteristics such as appearance, odour and unpleasant taste and, thus increasing the acceptance of the pharmaceutical formulation solid dosage form (22).

1.3.1. Fluidized bed equipment – Wurster process

Fluidized bed equipment is widely used for the coating of solid particles, such as granules, pellets and powders. The particles are fluidized by heated air, while a coating liquid is sprayed on them by a nozzle located at the bottom, horizontally or at the top in the device. Fluid bed equipment is categorized according to the nozzle location as bottom-spray, top spray and tangential spray. (23). Due to high temperatures, the solvent of the coating liquid evaporates and a solid film is formed, enclosing the particles (24).

The Wurster system is a bottom spray technique in which spraying is done from below to upwards, through a nozzle (figure 1.). The spray nozzle is integrated directly in the airflow (25), thus the droplets of the coating liquid only travel a small distance before contacting with the particles. The particles are carried out of the Wurster column (figure 1) on the air stream, which dries the coating film – spray drying- as the particles are lifted away from the nozzle and then fall down at the sides (26), which results in a defined repeated fluidized movement (fountain-like movement) (27). The fluidized movement continue on repeat until the film thickness goal is achieved (26).With the bottom spray technique it is possible to achieve a targeted and controlled movement of the particles (25). It has a specially designed air distribution plate (perforated). The different size holes in the perforated plate allow particles to flow pneumatically upward through the Wurster column and downward outside this column, allowing a cyclic particle flow passing in the spray zone (28). The most significant process variables are the volume and temperature of the inlet air, the atomizing air pressure and the coating liquid flow rate (29).

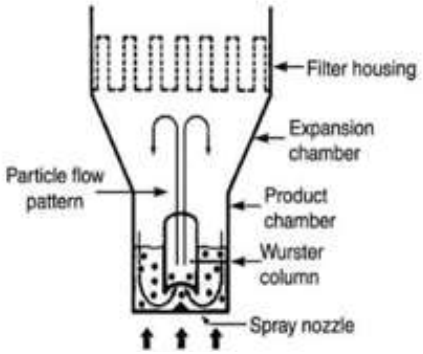

Figure 1. Schematic of a fluidized bed coating equipment - Bottom-spray using the Wurster configuration (26).

1.4. Milk as a novel excipient in paediatric formulations

The main and preferred route for drug delivery is the oral route. However, one of the biggest problems founded during formulation of orally administered drugs is the poor water solubility of some lipophilic drugs (e.g. NSAIDs, antibiotics, anti-cancer drugs and

antiretroviral drugs), that limits their oral bioavailability. The design of palatable pharmaceutical formulations for children is a crucial point in enhancing adherence to therapy by the child (6). However, this may sometimes present as a problem, since APIs bitter taste and sometimes associated gastric irritation make these drugs aversive and less acceptable, especially for paediatric population. Unlike adults, children cannot make conscious decisions over their natural perceptions and reactions and they are more sensitive to the unpleasant and unfamiliar taste of medicines than adults (30). Milk may represent the solution to these problems as it can function as a carrier of lipophilic drug molecules and its rich protein and fat components can be used to mask the bitter taste of several APIs, by its taste and by developing a physical barrier between the patient and the drug itself (30). From a regulatory aspect, milk has not been registered as an excipient. Despite that, milk is considered a basic food in many diets, presenting an established safety. Milk is a natural nutritive source, abundant and inexpensive, with desired characteristics for oral drug deliver. Moreover, it is a daily nutritive product for children (6), being the major source of energy, protein and fat for children (31) and having an immunological component that protects against several types of infections (6). It has been shown, that milk based formulations present improved pharmacokinetic characteristics, content uniformity (32), gastro protective and taste masking characteristics and also great solubilizing profiles. All these characteristics are extremely important in case of irritating, lipophilic and bitter-tasting drug substances (6). Regarding the gastrointestinal protective properties, literature recommends taking non-steroidal anti- inflammatory drugs with milk, to prevent gastric irritation that is caused by their cyclooxygenase (COX) inhibition mechanism. In fact, the ability of milk to prevent bleeding and stress-induced gastric lesions has been shown in studies performed in rats. The milk with higher fat content provided the greatest protection, while the skimmed milk the lowest. However, the evidence that the skimmed milk still presented some gastro protective properties, shows that milk's fat content is not the only component to have a gastro-protective effect. The mechanism of this positive effect was suggested to be related to the maintenance of a hydrophobic gastric surface that might enhance the barrier properties of the epithelium (33).

The use of lipid-based drug delivery systems, like milk, has emerged as a new approach to improve oral bioavailability of lipophilic drugs (34). Several reports in the literature have shown that the solubility of hydrophobic drug substances in milk is higher than their solubility in water. Moreover, studies with milk formulations with different APIs have shown higher dissolution rates, solubility and bioavailability when compared to traditional oral formulations of hydrophobic drugs (6).

1.4.1. Cow's milk composition

Milk can be classified according to its fat content in three categories, namely skimmed milk, half-fat milk and fat milk (31). The main components of milk are water, fat, proteins (casein and whey), lactose (disaccharide) and minerals. Milk's pH is normally between 6.5 and 6.7 at 25ºC (35). Milk is considered an oil-in-water emulsion due to its fat content, a suspension due to its proteins content and a solution because of the lactose and minerals (35). Fat in milk exists in the form of small globules with diameters between 0.1 to 20 μm. These small fat globules are composed of triglycerides - which are the major component - monoglycerides and diglycerides, fatty acids, sterols, carotenoids, vitamins A, D, E and K and trace elements. Carotenoids are responsible for the yellow-light colour of the milk. The membrane of these small fat globules is composed of phospholipids, lipoproteins, cerebrosides, proteins, nucleic acids, enzymes, trace elements and water (35). Milk fat globules change the state from solid to liquid at 40°C (36).

Casein and whey are two different proteins present in milk. Casein represents 80% of milk protein content (37) and has an average diameter of 200nm (38). It is subdivided into five groups, alpha1, alpha2, beta, gamma and kappa caseins (37) and is included in the list of *Generally Recognized As Safe* (GRAS) substances (6). Casein proteins act as a surface-active agent, due to the presence of hydrophobic and hydrophilic regions in its amino acids and, this way, they are able to form micelles (39). It has been described in the literature that a lipophilic drug can be entrapped by the casein micelles. Due to casein's surface-active properties, there is an increase in the solubility of lipophilic drugs in gastric media, when orally administered, hence improving the drug bioavailability (37) and reducing the interaction with the sensory receptors, consequentially decreasing the perception of bitterness (40). Casein micelles have porous in their structure that allow the release of the entrapped drug substance from the micelle into the dissolution media (37). Casein micelles can form complexes in milk with calcium and magnesium by interaction with its hydroxyl groups (41). Whey proteins englobe beta-lactoglobulin, alpha-lactoalbumin, bovine serum albumin and immunoglobins. These proteins present better solubility than casein proteins (37) and also have surface active properties (42).

Another component of the milk is lactose, which is its main carbohydrate. Lactose is a disaccharide composed by two monosaccharides: glucose and galactose and plays a role in the intestinal absorption of magnesium, calcium and phosphorus, and also in the utilization of vitamin D (31).

Milk viscosity and density is dependent from the temperature and fat content. Milk's viscosity varies exponentially with the temperature and linearly with the lipid content. Studies have shown that milk's viscosity and density decreases with the increase of temperature (36).

Disadvantages of using milk as excipient include cases of milk intolerance or milk hypersensitivity. Milk intolerance is caused by lactose. It has a non-immunological cause and is rarely associated with intestinal injury (31). β-galactosidase is an enzyme required to hydrolyse lactose into a simpler sugar, making it possible for humans to digest and then absorb these sugars. The lack of this enzyme may lead to the appearance of several symptoms such as abdominal pain, nausea, diarrhoea and flatulence. The symptoms severity depends on the characteristics of each individual, on the degree of lactase deficiency, the quantity of lactose ingested and the form of lactose ingestion (43). Almost 70% of the world's population has some degree of lactose intolerance. The percentage of lactose intolerance among different populations depends on several factors such as ethnicity and dairy products traditionally included in their diet, leading to a genetic selection for the ability to digest lactose (43). In contrast, milk hypersensitivity involves the immune system and causes different degrees of injury to the surface of the intestinal mucosa (31). Milk's allergy is an immunological reaction mediated by IgE and it may cause cutaneous, gastro-intestinal and respiratory reactions and, in extreme cases, an anaphylactic reaction (31).

1.5. Paracetamol (acetaminophen)

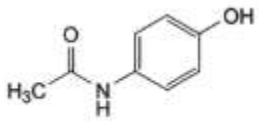

Figure 2.Chemical structure of paracetamol.

Paracetamol is one of the most popular and widely used analgesic and antipyretic drug. It is commonly used for the treatment of pain and fever among paediatric population (44) and is considered as first-line therapy for the treatment of both clinical manifestations, according to international guidelines and recommendations (45). Paracetamol is indicated by the WHO *Model List of Essential Medicines for Children* as medicine for pain and palliative care and also as antimigraine (4). Its mechanism of action is not totally understood but it is believed that it may inhibit the nitric oxide (NO) pathway mediated by several neurotransmitters, thus reducing the pain. Its antipyretic activity is believed to result from the inhibition of prostaglandin synthesis and release into the central nervous system (CNS), thus acting on the prostaglandin-

mediated effects on the heat-regulating centre in the anterior hypothalamus (46). It is normally considered to be effective, safe and well tolerated in recommended doses. Paracetamol is metabolized in the liver (45) and its toxicity is closely connected to its metabolism (44). In cases of overdose, paracetamol causes hepatotoxicity, and in extreme cases it can cause acute liver injury and even liver failure and hence death (46). Paracetamol is a lipophilic active substance. It is classified as a weak acid, having a pKa of 9.38 at 25ºC, therefore its absorption in the stomach is minimal, due to the acid environment. It is mainly absorbed in the intestine, with a bioavailability of almost 90%, presenting as a non-ionic form. As soon as paracetamol reaches the basic environment of the duodenum, it is quickly absorbed and enters the bloodstream. Paracetamol presents a small binding percentage to plasma proteins (10-25%), which is an important characteristic that differentiates Paracetamol from other analgesics and antipyretic drugs, such as Ibuprofen (45). The dose to administer should be adjusted to the age and weight (mg/kg) of the child. Every clinical factor or concomitant medications that may increase the risk of toxicity must be considered (45). For pain- mild to moderate- or fever the maximum daily dose is 75 mg/kg/day, for children, divided into 5 doses. Doses may be repeated every 4h, maximum of 5 doses per day. For children below 2 years old is recommended 15mg/kg/dose every 6h and a maximum daily dose of 60mg/kg/day (47). Physical and chemical properties of paracetamol are described in the following table:

Table 1.Paracetamol properties.

Empirical formula	**C8H9NO2** (48)
Molecular weight (g/mol)	151.2 (48)
Melting-point (ºC)	168 to 172 (48)
Boiling point (ºC)	500 (48)
Density (g/cm3)	1.3 (48)
Solubility (mg/L) at 25 °C	Slightly soluble in water; soluble in 96% ethanol (48)
pKa	9.38 (48)
Wavelength of maximum absorption (nm)	249 (48)
Organoleptic characteristics	White or almost crystalline powder(46,48), odourless, slightly bitter taste (46)

2. AIM OF THE PROJECT

The purpose of this investigation was to evaluate the ability of milk to function as film-forming and taste-masking agent, in a formulation designed specifically to paediatric population. Three types of cow's milk - skimmed milk, half-fat milk and fat milk- were evaluated as an excipient (coating agent) for pellets manufacturing for their capacity to functioning as film forming agents, in order to mask APIs bitter-taste.

3. MATERIALS AND METHODS

3.1. Materials

Pellet cores made with Paracetamol (batch: 14112111; Company: Novacyl) and Microcrystalline Cellulose (Avicel ® PH101 – batch 60746C; Company: FMC) were coated with three different types of cow's milk – skimmed milk, half-fat milk and fat milk. All types of milk were obtained commercially from Esselunga, Italy. The composition of each type of milk are described in table 2.

Table 2.Classification and composition of different types of fresh milk based on fat content.

Type of Milk	Lipids (g)	Proteins (g)	Carbohydrates (g)	Salt (g)	Calcium (g)
Skimmed milk	0.5	3.3	4.9	0.13	0.120
Half-fat milk	1.6	3.2	5.0	0.1	0.120
Fat milk	3.6	3.2	4.8	0.13	0.120

The values refer to 100mL. The information was taken from the labels of the *Esselunga* brand milk packaging.

Pellets cores with Paracetamol (batch: 14112111; Company: Novacyl) and Microcrystalline Cellulose (Avicel ® PH101 – batch 60746C; Company: FMC) were made as control.

3.2. Methods

3.2.1. Preparation of pellets

Pellet cores with 70% of Paracetamol, 30% of Microcrystalline Cellulose and deionized water as binder were made by extrusion-spheronization in order to study the ability of different types of milk to function as film-forming agent. For core's preparation, microcrystalline cellulose and paracetamol were mixed using a planetary mixer Kenwood®, KM200, UK, where the binder solution was slowly added in an appropriate quantity during constant mixing for 5 min. Then the wet mass was extruded in NICA®system. Finally, the extrudates were placed in a spheronizer NICA® 5320 with a groove plate (d=64cm) at 700 rpm for 5min in order to obtain pellets. In the end, pellets were dried in an oven PID ®System, type M120-VF at 40ºC for 24h.

3.2.2. Coating in fluidized bed equipment using Wurster process

The coating process was performed in fluidized bed MiniGlatt ®, using the Wurster configuration. Three coating films were made, one of skimmed milk, another of half-fat milk and a third using fat milk. The composition of each coating liquid is described in table 2. The

volume of each coating liquid needed to achieve a final weight gain of 30% was calculated. The total volume value was obtained taking into account the weight of solids of each type of milk (table 2.), so that all coating films had the same weight of solids.

For the coating process, 75mg of pellets with a size range between 850-1000 µm were weighted. The spraying was done from below to upwards, through a nozzle with 0.5mm of diameter. The coating liquid was pumped continuously into the fluidized bed by a Watson-Marlow ® pump. The coating parameters values used in each coating process are described in table 3.

Table 3.Coating parameters values used for each coating formulation – skimmed milk, half-fat milk and fat milk.

Coating formulation	Skimmed milk	Half-fat milk	Fat milk
Temperature of inlet air (ºC)	66-70	62-65	65-70
Volume of inlet air (m^3/h)	21-24	19-22	18-23
Product Temperature (ºC)	38-41.8	38-41.6	37-41.0
Atomizing air pressure (bar)	1-1.2	1-1.2	1-1.12
Velocity of Pump (rpm)	2-4	2-4	2-3

The coating process ended when the coating liquid finished. After the coating process, pellets were kept inside the spray/decompression house of the MiniGlatt® for 10 min, with the same parameters values that had been used during the coating process (table 3.), for drying and stabilize the coating layer.

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3.2.3. Calibration curve

The calibration curve was prepared using a spectrophotometer UV/VIS Lambda® 35, PerkinElmer at a wavelength of 243 nm. 0,2mg/mL stock solution was prepared dissolving 20mg of Paracetamol in 100mL deionized water. Withdrawals were made using 10 and 15 mL graduate pipettes, and diluted appropriately to obtain 0.02, 0.04, 0.08, 0.12 mg/mL solutions. Final solutions were analysed in the spectrophotometer using 1cm cells of quartz. The curve (Figure 3.) was subsequently constructed to obtain the concentrations of paracetamol of each sample once the absorbance of these samples had been measured.

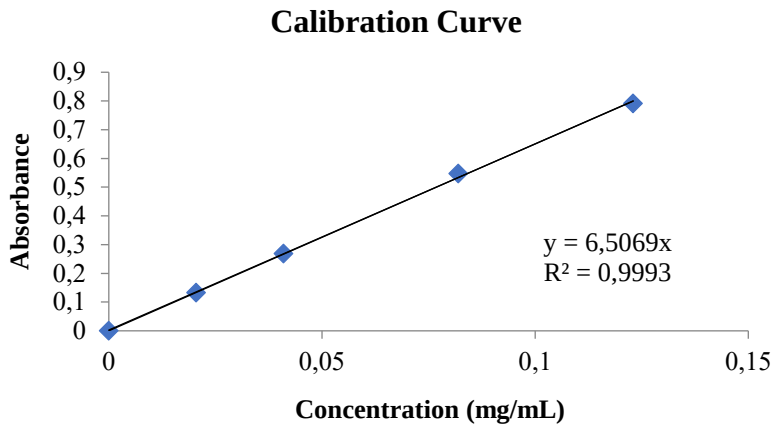

Figure 3.Calibration curve of Paracetamol.

3.2.4. Percent product yield

Percent product yield was calculated subtracting the weight of agglomerates formed from the final pellets weight, as the following formula demonstrates:

$$Percent\ yield = \frac{total\ amount\ of\ coated\ pellets\ (g) - agglomerates\ (g)}{total\ amount\ of\ coated\ pellets\ (g)} \times 100 \quad (1)$$

The amount of agglomerated pellets was established upon visual inspection of pellets during sieve analysis. Particles with a size bigger than 1180 µm that appeared to be agglomerates of at least 2 units were subtracted from the total amount of coated pellets to obtain the non-agglomerated product.

3.3. Characterization of the coated pellets

3.3.1. Size and size distribution (sieve analysis)

Size and size distribution of pellets was done using a mechanical shaker Endecotts Octagon® 200, UK, subject to agitation - amplitude 4, 5min - and sieves ASTM® standard with mesh between 500 and 1400µm of aperture. The sample was mechanically shook through a serie of successively smaller sieves, and the fraction of the sample remaining on each sieve was weighted.

3.3.2. Loss on drying

The loss on drying was measured by heating a sample of each batch at 110 ºC, on a heating Mettler® Italia, LP15. The weight of the sample was monitored until it became constant.

Loss on drying was calculated using the following formula:

$$LOD\ (\%) = \frac{Weight\ loss\ (g)}{Inicial\ \ weight\ (g)} \times 100 \quad (2)$$

3.3.3. Friability

The friability of pellets was analyzed using a mechanical mixer Turbula® Willy A. Bachofen Maschinenfabrik, Friability was tested at 200rpm for 10 min. A sample of 10g of pellets was introduced into a glass container of 100ml together with 10 glass spheres with a diameter of 7mm and a total mass of 10 g. The glass container was placed into a horizontal mechanical mixer and stirred for 10 min at 200rpm. Subsequently, the sample passed through a sieve with a mesh of 250 µm. After removing the dust, the friability was calculated from weight loss before and after the analysis. The friability value was obtained by using the following formula:

$$Friability\ (\%) = \frac{Weight\ loss\ (g)}{Inicial\ \ weight\ (g)} \times 100 \quad (3)$$

3.3.4. Dissolution tests

The drug release from pellets was analysed using a dissolution apparatus (paddle method, 100 rpm, at 37,0 ±0,5ºC, Distek® Dissolution System 2100B, USA). The test was carried out on samples of 300mg pellets. The dissolution medium consisted of 900mL of deionised water with the specifications of the European Pharmacopeia 9 (49). Samples were collected at predetermined times and then analysed in the UV Spectrophotometer Lambda®, PerkinElmer 25. I (λ=243 nm,1cm quartz cell) in duplicates.

3.3.5. Drug Content (Assay)

Drug content of Paracetamol pellets was analysed spectrophotometrically, using a UV/VIS Lambda® 35, PerkinElmer spectrophotometer at a wavelength of 243 nm. Samples of each batch (50mg, corresponding to 35mg of paracetamol) were weighted and smashed prior to dilution in 100 mL water. Withdrawals were made using 10mL graduate pipettes and diluted in 50mL volumetric flasks. Between the two dilutions the samples were homogenised in an Ultra-Turrax® for 15min and filtered twice through a 0.45µm membrane filter. The

concentration of drug was determined by measuring the absorbance in the UV-visible spectrophotometer (λ=243 nm, 1cm quartz cells).

3.3.6. Aspect Ratio

For the aspect ratio analysis, 20 pellets of each batch were randomly analysed with Dino-Lite® Digital Microscope Pro which is a digital microscope that works with a Dinocapture 2.0. system. The image obtained in the microscope was processed by a software ImageJ that measures the major axes and the minor axes of the pellets and calculated the aspect ratio as a ratio between these two axes.

3.3.7. Scanning Electron Microscopy

Morphology of pellet's surface and film thickness of the coated pellets were qualitatively analysed by scanning electron microscopy (SEM; LEO 1430, Carl Zeiss, Germany). Samples were gold-sputtered using a plasma evaporator under vacuum (Nanotech sputter coater with argon, 10 mA, vacuum 80mTorr, for 3 min), and photomicrographs were acquired at an accelerated voltage of 10 kV at differing magnifications. The cross-sections were obtained cutting the coated pellets with a blade.

4. RESULTS AND DISCUSSION

During the coating process in the fluidized bed equipment, regardless of the type of milk present in the coating formulation, pellets tended to stick to the equipment wall, to the nozzle and to the filters, forcing the interruption of the process frequently to clean the equipment. Furthermore, there was also a massive accumulation of powders in the filters. During the process a large amount of agglomerates was detected. The volume and, consequentially, the temperature of the air inlet was not constant during the coating process (table 3) and had to be adjusted manually. In general, the fluid bed process was not stable.

A batch, with the same composition, size range and without coating layer was made to function as control. This batch were characterized in terms of drug content, loss on drying, friability, loss on drying and dissolution rate with the same techniques as the coated pellets.

4.1. Preliminary study

Since there was no reference in the literature concerning the use of fresh milk as a film-forming agent, a preliminary batch of pellets with the same composition and size range - 850 to 1000μm- of the pellets used in the coating with different types of milk, was used to set the values of the parameters -inlet air temperature and volume, product temperature, atomizing air pressure and velocity of the pump- for the coating process. The values of the parameters were optimized by trial and error in order to obtain a correct fluidized movement (similar to a *fountain flow*) (27) of the pellets. This movement was accomplished with the values described in table 4. The test was performed for 10min using a half-fat milk as coating liquid.

From the values obtained in the preliminary study it was possible to narrow the range of values for the parameters to be used in the coating process with the different types of milk.

Table 4.Coating parameters values obtained in a preliminary study.

Parameters	
Temperature of inlet air (ºC)	65-66
Volume of inlet air (m^3/h)	20
Product temperature (ºC)	39-40
Atomizing air pressure (bar)	1-1.2
Velocity of Pump (rpm)	2-4

4.2. Coating process with different types of milk

In the spray drying technique, when the water is removed from the milk, a number of phenomena happen. The content of solids increases, as well as the viscosity and surface tension (50). Milk's components move closer and the probability of interaction is higher, the quantity of calcium (38) and whey proteins associated with casein micelles increase, pH decreases (51) and the fat globules membrane are disrupted during the atomization (52) .

Maintaining the volume of the inlet air constant during the process was a critical difficulty. Due to the tackiness of the coating film, pellets tended to adhered to the equipment, blocking the nozzle and thus decreasing the spray rate, forcing an increasing on the volume of the inlet air. Moreover, as agglomerates were forming, the particles became heavier and the necessity to increase airflow was higher. However, an excessively high volume of inlet air increased the brittleness of the cores and led to the formation of cracks on the coating layer (53). These effects were possible to verify by SEM images (Figure 4.).

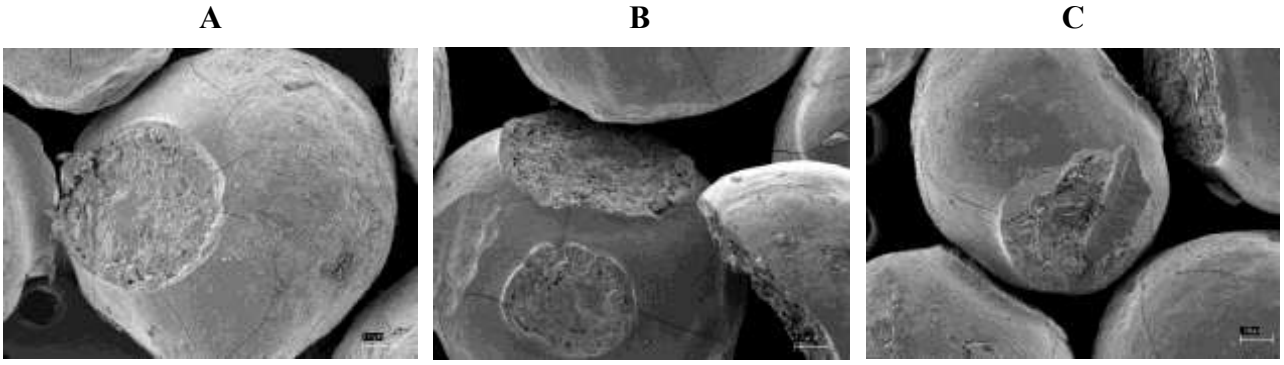

Figure 4.SEM images of coated pellets. A: Coating with skimmed milk; B- Coating with half-fat milk; C- Coating with fat milk.

When the volume of air inlet was too low, the agglomeration was higher due to the fact that the flow was not enough to provide circulating air for the coating drying (53). Agglomerates behave as larger particles. Therefore, the agglomerates raised slower than the non-agglomerate particles falling down and, thus blocking the nozzle (54), resulting in a non-homogenous coating process, which led to coated particles with different sizes inside the same formulation, as it was possible to verify by size distribution analysis (Figure 5.). Moreover, frequent changes in the volume of the air flow resulted in a heterogenous contact between the coating film droplets and the pellets, contributing to a heterogeneous coating process. For these reasons, the size distribution range inside the same formulation was bigger than expected. It was expected that all coated pellets had the same size inside the same formulation. Also related with sieve analysis, a larger amount of agglomerates was detected during the coating with fat milk due to its higher fat content (Table 2.), which led to a more heterogenous coating process, explaining

the widest range of the coated particles sizes obtained (Figure 5.). The milk's fat globule membrane prevents the lipidic globules from coalescing and acts as an emulsion stabilizer (55). However, during the atomization, the membrane are disrupted, increasing the fat surface and consequently causing sticking problems (35), which resulted in an increased agglomeration formation (56).

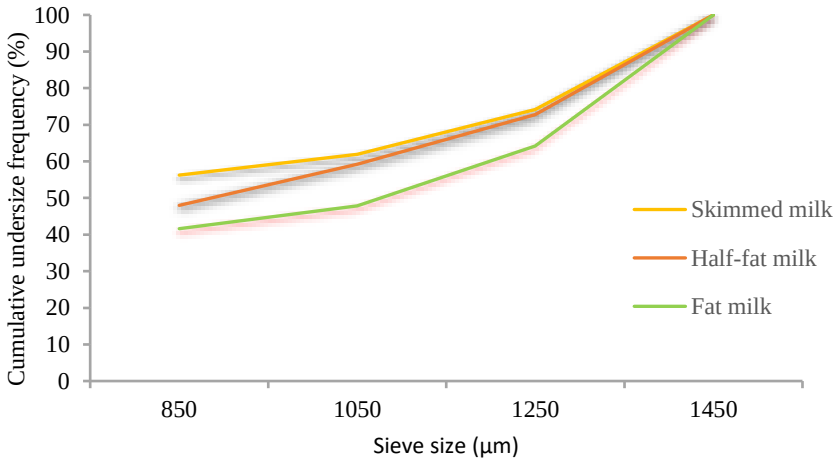

Figure 5.Particle size granulometry (cumulative volume %) of coated pellets from each coating-film formulation.

In order to prevent tackiness of the film coating and to reduce agglomeration of the particles during the coating process, an anti-adherent, such as talc, can be added to the coating formulation (26). Talc is a hydrophobic anti-adherent used extensively in film coating formulations. It has been evidenced by its properties to improve the surface smoothness of the coating film and to avoid stickiness (57). The particle size may vary according to the suppliers. Studies have shown that bigger talc particles can cause a more brittle film when compared with smaller talc particles (58).

Another difficulty encountered during the process was maintaining the temperature of the product stable. The temperature of the product was not directly adjustable, although it was influenced by the temperature and volume of the inlet air, which were adjustable parameters (59). As the airflow rate was increased, the temperature of the product decreased, arising the necessity to increase the temperature of the inlet air to maintain the temperature of the product constant. When the temperature of the product was too low, pellets showed the tendency to form agglomerates. This was due to the fact that with the decreasing of temperature, milk's viscosity increases (36) thus, the tendency to form agglomerates is higher. Bellow 40°C, milk's fat globules have the tendency to agglutinate and some caseins – specifically β-casein –

disassociate from micelles, which causes an increase in viscosity (60). Furthermore, the lower temperature did not allow the coating liquid to dry as well as expected, resulting in over wetting of the pellets which led to sticky pellets that blocked the nozzle and adhered to the filters and walls. In contrast, high temperatures may cause the drying of coating droplets before they reach the pellets cores, resulting in massive loss of coating material and, consequentially, a thinner coating layer (53). For this reason, the filters were frequently full of powders, forcing the interruption of the process in order to clean them.

Variations of the temperature during the process contributed to the formation of cracks on the film, due to internal stress caused by the quick evaporation of the coating liquid's solvent (61) . The addition of a plasticizer to the coating film should reduce the intermolecular strength between the proteins of milk and decrease the internal stress, increasing the flexibility of milk's polymeric components and this way reducing the incidence of cracking (62). The glass transition temperature (Tg) of proteins increases with chain rigidity. Plasticizers decrease the Tg of the film, facilitating the molecular mobility. It has been described in literature that the presence of sorbitol has a plasticizing effect on calcium caseinate films. This plasticizer effect is attributed to the presence of hydroxyl groups, resulting in the formation of sorbitol-caseinate interactions, resulting in more flexibility in the polymer chain. Also, the presence of a plasticizer in the calcium caseinate film decreased the viscosity of the film-forming formulation (63) .

The yield results ranged between 50 and 64% (Table 5.). These values can be explained by the large amount of agglomerates formed and the massive loss of coating liquid that turned into powder during the coating process. The formulation with fat milk as coating liquid showed the lower yield (50%). Fat milk has a higher lipidic content (35) and higher viscosity (64), thus increasing the stickiness of the coating liquid and, this way, forming a higher amount of agglomerates.

Concerning the process length, the shortest process was the coating with fat milk, followed by the half-fat milk and finally the coating with skimmed milk, which was the longest process (table5). Calculations for the volume needed to achieve the 30% of weight were made, so that all the three coating films had the same amount of solids. Fat milk has the highest amount of solids (table2) due to its fat content (35), thus it needs less volume to achieve the same weight of solids of the other coating formulations.

Table 5.Classification parameters of the coating process with skimmed milk, half-fat milk and fat milk. Control: uncoated pellets with the same nuclei composition and same granulometric class.

Film-coating	Skimmed milk	Half-fat milk	Fat milk	Uncoated
Coating liquid weight (g)	256.4	225.4	185.0	--
Process length (min)	165.0	141.0	123.0	--
Weight gain (%)	28.3	22.0	28.7	--
Drug content (%)	75.3	75.0	77.7	103.6
Product yield (%)	64.3	59.6	50.2	--
Loss on Drying (%)	1.2	1.3	1.3	1.2
Friability (%)	0.3	0.3	0.3	0.1
Aspect Ratio	1.1	1.1	1.12	1.12

By the analysis of the drug content, was possible to note a decreasing of drug content in all formulations when compared with the uncoated pellets (Table 5.). However, between each formulation the value obtained was very similar (Table 5.). This means that probably, the coating layer trapped the API -paracetamol- making impossible the complete extraction of the API. Casein is a protein present in milk that acts as a surface-active agent, forming micelles (39). It has been described in the literature that casein micelles entrap lipophilic drugs (37). Paracetamol is slightly soluble in water (48), therefore, it may have been entrapped in casein micelles. Possibly, the drug content technique utilized did not allowed the complete extraction of the paracetamol from the casein micelle., explaining the low values of drug content. This result may prove that milk can function as a drug deliver carrier, improving the bioavailability and masking the bitterness of the API. Since all three coating liquids have different fat contents, and the drug content value was similar in all three formulations, this might mean that the fat content has no significant influence on the drug content test. To improve the creditability of the drug content test, the blank should be treated in the same manner as the paracetamol formulation and used to minimize the interference of proteins present in milk (42).

Friability and loss on drying were investigated to evaluate and compare the coated pellets with the uncoated- control batch. The coating layer did not have a significant impact on these results (table5). The friability percentage increased 0.2%, not representing a significant change. Although loss on drying did not suffer significant changes (table 5.) when comparing coated pellets with the uncoated pellets, after this test it was possible to verify that pellets coated

with half-fat milk and fat milk were agglomerated and sticky. This phenomena can be explained by the fact that milk's fat content melts from 22°C to 36°C (65) and the test was performed at 110°C. Pellets coated with fat milk were the ones where this phenomenon was the most evident, due to its higher fat content (table 2.).

Concerning the aspect ratio analysis, the optimal value for this test is 1.0, however values until 1.2 also indicate a satisfactory pellet shape (66). The values obtained for aspect ratio range from 1.1 to 1.2, indicating a spherical shape, concordantly upon visual inspection (figure 6.). Scanning electron microscopy qualitative investigation revealed a surface morphology nearly spherical (figure 4.) – confirming the aspect ratio value (figure 6.) - though full of cracks.

Figure 6.Aspect ratio images for each coated formulation: skimmed milk (A); half-fat milk (B) and fat milk (C).

The dissolution rate did not change with the coating film, as it was possible to observe by the overlapping of both coated and uncoated pellets dissolution curves (Figure 7). The drug release was complete within 90min. Although powder milk has a high reconstitution rate in water (67), this result may support the idea that the coating layer was not efficient, confirmed through visual evaluation of the cross-section cut in SEM images (Figure 4.),that revealed a coating layer with a small thickness in every coating formulation, contradicting the weight gain accomplished in each formulation (Table 5).

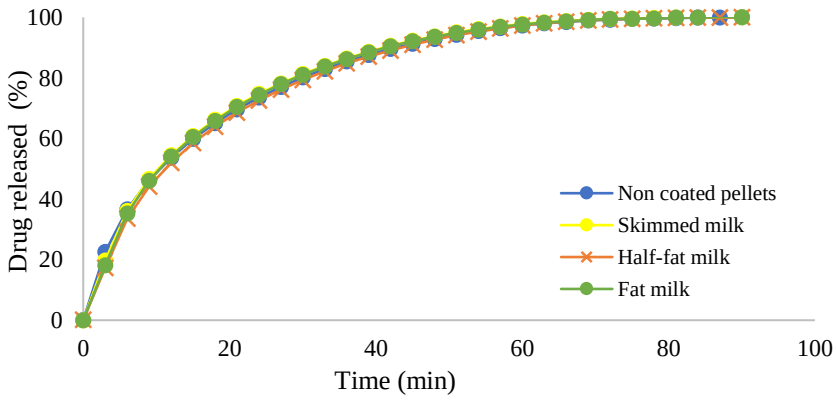

Figure 7.Dissolution profile of paracetamol from pellets with different coating films and from the uncoated pellets.

The organoleptic characteristics of the coated pellets were analysed. Coated pellets were light-yellow, with the characteristic odour and taste of milk. These results showed that the coating process was complete and that milk can actually function as a taste mask agent.

5. CONCLUSION

Combining the results and findings from all the research it might be possible to postulate the ability of milk to function as film-forming, and thus taste-masking agent. A drug content between 75-78 % was achieved, indicating that milk might be able to function as drug carrier of lipophilic drug substances. Moreover, milk develop a barrier between the bitter-taste of the drug substance and the receptor by trapping the active ingredient. This idea was supported by the analysis of the organoleptic characteristics of the coated pellets which taste, colour and smell was characteristic of the milk.

The high tackiness of the coating formulation and the volume of inlet air were found to be the most critical variables of the coating process.

The yield results ranged between 50 % and 64 %. Formulation with fat milk as coating liquid had the lower yield, due to the high lipid content that resulted in a higher formation of agglomerates. The tackiness of the coating liquid, the inconstant air flow rate and temperature of the product led to an heterogenous coating layer, resulting in different sizes of pellets inside the same formulation. Aspect ratio, friability and loss on drying did not suffered significant changes with the addition of the coating layer.

The value of weight gain accomplished for each formulation was an error with unknown cause. This fact was supported by the SEM images and the dissolution profile.

6. FUTURE WORK

A formulation of milk without lactose could be developed. Lactose intolerance affects almost 70 % of the world's population (43) and the development of lactose free products is an increasing trend in food's market (68).

Milk, for its content in casein and whey, might be considered as a potential natural film coating agent as a substitute for synthetic polymers.

New and improve coating formulations using fresh milk as an excipient can be developed. An anti-adherent could be incorporated in this formulation in order to solve the tackiness problem inherent to milk, for example, talc. Talc is a hydrophobic compound and thus, compatible with milk. It has been described in literature that formulations containing talc shown less agglomeration formation during the coating process than the coating formulations without talc. Furthermore, the addition of a plasticizer to the formulation could avoid brittleness of the coating film and consequently cracks on pellets surface. Sorbitol is a plasticizer reported in literature, with significant effect on caseinate films (63).

Thus, the optimization of the air flow rate and the temperature at drying temperature of the coating liquid will decrease the tackiness problems (23), as well as the improvement of the coating formulation, might increase the stability of the coating process variables, increasing the coating-film quality and uniformity.

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